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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/882,509	06/15/2001	Mosuvan Kuppusamy	51321-003	8339

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EXAMINER	
MONSHIPOURI, MARYAM	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/882,509	KUPPUSAMY ET AL.	
	Examiner	Art Unit	
	Maryam Monshipouri	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *6 and 12-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date Filed. 2/12/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's response to restriction requirement filed 11/5/2003 is acknowledged. Applicant elected Group I invention directed to claims 1-5 and 7-21 with traverse. Claim 6 is withdrawn as drawn to non-elected invention.

In traversal of restriction requirement applicant argues the following: **(1)** the examiner has not carried the burden of providing any reasons and/or examples for concluding that the claims of the restricted groups are patentably distinct. Applicant then continues by indicating that examiner's statement that "each method has different steps and different end-points" is insufficient to support the conclusion that the claims are patentably distinct. Applicant further adds he/she is unclear as to how the additional co-transformation step of the host cell with BRP gene in claim 6, renders the invention patentably distinct from, say claim 4. Furthermore, according to applicant, the goal (or the end-point) of all method claims is to produce enzymatically active streptokinase. Thus, it is unclear how the Office can conclude that the end point of claim 6 is different than the end-point of claim 4.

(2) Since both Groups I and II are classified in class 435, subclass 194 no additional burden of examining is placed on the Office in examining all pending claims because a search of Group I will necessarily be co-extensive with a search for that of Group II and therefore restriction should be withdrawn.

Applicant concludes but reserving his/her right under In re Ochiai to seek rejoinder of non-elected claims when those claims relate to a process of making or using no obvious products.

These arguments were fully considered but were found **unpersuasive.** With respect to applicant's **first** argument the examiner respectfully maintains that in contrast to applicant's view the criteria of different steps and different end-points is totally sufficient and convincing under 35 U.S.C. section 121, to render method inventions patentably distinct from each other. Applicant is well aware that claim 4 as written is producing inclusion bodies within the host cell and therefore has inclusion bodies as the end-point. While in claim 6, he/she is producing soluble active streptokinase in free solution as the end-point. Therefore, as applicant can appreciate the end-points of claims 4 and 6 are functionally and structurally different. Further, method of claim 6 has steps that are totally irrelevant and unnecessary for method of claim 4. Applicant is respectfully required to note the term "another DNA expression construct" in claim 6, implying that that DNA construct of claim 1 (used in claim 4) is no longer used in claim 6. Thus, the examiner is puzzled as to how applicant does not find that methods of claims 4 and 6 , which clearly have different steps and different end-points, patentably distinct. In fact, the examiner is of the opinion the dependency of claim 6 (as currently written) from claim 4 may be improper as the method of making soluble secreted streptokinase (claim 6) cannot logically depend from method of making inclusion bodies, which produce insoluble enzyme (claim 4).

In response to applicant's **second** argument, the examiner maintains that even though there may be some overlap between the searches required for each invention, said searches in contrast to applicant's view are **not coextensive**. The search required for invention of Group I requires for searching host cells and constructs that are suitable

of producing streptokinase in inclusion bodies, as well as a search in class 536/23.2. Said requirement is totally unnecessary for Group II invention, independently requiring an additional search for BRP genes etc. (class 536/23.1), which in their turn are irrelevant to the search required for Group I invention.

Therefore, in view of the above response in addition to arguments provided previously, restriction is maintained and is hereby made **final.**

The office will consider rejoinder of non-elected claims relating to processes of making and using allowable products according to *re Ochiai* if such situation arises.

Upon further review of the previous office action it is noted that claims 12-21 have been erroneously grouped with Group I invention and said claims should have been part of Group II invention. The examiner apologizes for any inconvenience that said error must have caused the applicant. Claims 6 and 12-21 are hereby withdrawn as drawn to non-elected invention.

DEATAILED ACTION

Claims 1-5, and 7-11 are under examination on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-5, 7-13, 15-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In claim 1 (and its dependent claims 2, 4-5 and 7) applicant is claiming a **genus** of products (namely streptokinsae) and methods of use thereof that have not been adequately described in the specification.

The court of Appeals for the Federal Circuit has recently held that such a general definition does not meet the requirements of 35 U.S.C. 112, first paragraph. " A written description of an invention involving chemical genus, like a description of a chemical species, requires a precise definition, such as be structure, formula {or} chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The court held that " in claims involving chemical materials, generic formulae usually indicate with specificity what generic claims encompass. One skilled in the art can distinguish such a formula fro others and can identify many of the species that the claims encompass. accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish it from others. One skilled in the art therefore cannot, as one can do with a fully described genus visualize the identity of the members of the genus". Here, applicant is claiming constructs comprising a genus of streptokinases from any sources and species that are merely defined by function. The

specification does not teach how much structural homology exists among all members of the genus such that skilled artisan can distinguish claimed genus from others. All applicant provides is a **single species** (namely SEQ ID NO:3) which is insufficient o pout the skilled artisan in possession of all members of the genus.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term " λpR-λpL" in claim 2 is unclear. Applicant has not explained this term structurally in the specification. It is unclear as to how said promoter is different than the ones in the prior art.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "as compared to sterptokinase production in the host cell when the host cell is not heat induced" is unclear. It is not clear how said phrase contributes to the claimed subject matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Pang (U.S. Patent No. 5,011,686, issued 4/1991) teaches a DNA construct (see column 10, pBr322 plastid to form pR6) comprising in 5' to 3' order, the promoter operationally linked to a DNA encoding streptokinase from *Steptococcus equisimils* which inherently has SEQ ID NO:3 of this invention, as it is originating from the same source. Said DNA construct inherently drives formation of inclusion bodies in a host cell, because it is structurally very similar to that produced for urokinase (see Example 2), that successfully formed inclusion bodies in E. coli, rendering claims 1 and 3 anticipated.

Claims 1-5, 8-9, 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Pupo et al. (Biotechnology Letters, 21, 1119-1123, 1999). Pupo teaches a DNA expression construct (see vector pACS-2, page 1120) comprising the streptokinase (skc-2) gene from *S. equisimilis* (ATCC 9542), which inherently has SEQ ID NO:3, because it originates from the same source as SEQ ID NO:3 and inherently drives formation of inclusion bodies comprising enzymatically active streptokinase (anticipating claims 1-3), genetically engineered host cells (E. coil, see Materials and methods section), comprising said DNA expression constructs, anticipating claim 11, and methods of producing streptokinase using said products whereby the host cell expresses inclusion bodies comprising enzymatically active streptokinase (see figure 2) ,anticipating claims 4-5) optionally further comprising inoculating the culture media with

said host cell and optionally comprising isolation of said enzymatically active sterptokinase (anticipating claims 8-9) .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-5, 8-11 are rejected under 35 U.S.C. U.S.C. 103(a) as obvious over Pang (mentioned previously) in view of Marston (Bio/technology, 2, 800-804, 1984, cited in the IDS). As mentioned above, Pang teaches a DNA construct (see column 10, pBR322 plasmid to form pR6) comprising in 5' to 3' order, the promoter operationally linked to a DNA encoding streptokinase from *Steptococcus equisimils* which inherently has SEQ ID NO:3 of this invention further comprising a promoter that inherently drives formation of inclusion bodies comprising said streptokinase in a host cell. Pang neither teaches genetically engineered host cells transformed with its specific DNA construct nor teaches methods of producing streptokinase in inclusion bodies optionally comprising purification steps recited in claim 10.

Marston teaches about solubilization of prochymosin synthesized in inclusion bodies in E. coli, indicating various steps of pelleting of transformed E. coli, (see Experimental protocol) followed by lysing thereof, isolation and solubilization of inclusion bodies, diafilteration of inclusion bodies, purification of said diafiltered products by ion-exchange chromatography etc.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to start with DNA construct of Pang and transform a host cell (such as E. coli) as taught by Pang in the case of urokinase conjugate expression (see Example 2) in order to express the streptokinase conjugate of Pang, which could later be used to inoculate a fermentation media for large scale fermentation of said streptokinase followed by purification of said streptokinase (formed in inclusion bodies) according to teachings of Marsten.

One of ordinary skill in the art is motivated in obtaining a genetically engineered host comprising large amounts of streptokinase conjugate of Pang and fermenting it before isolating the streptokinase from inclusion bodies, according to Marsten because streptokinase conjugate of Pang (having analgesic properties) can target streptokinase to the blood clot area for treatment of patients with heart problems, rendering the invention obvious.

Finally, one of ordinary skill in the art has a reasonable expectation of success in producing said genetically engineered host cell and fermenting it for production of said streptokinase conjugate because methods of transforming host cells and using said products in preparation of streptokinase in inclusion bodies optionally comprising the purification steps of claim 10 are well established in the prior art, as evidenced by teachings of Pang in view of Marsten.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maryam Monshipouri whose telephone number is (571)

272-0932. The examiner can normally be reached on 7:00 a.m to 4:30 p.m. except for alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnanthapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maryam Monshipouri Ph.D.

Primary Examiner

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